Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A])

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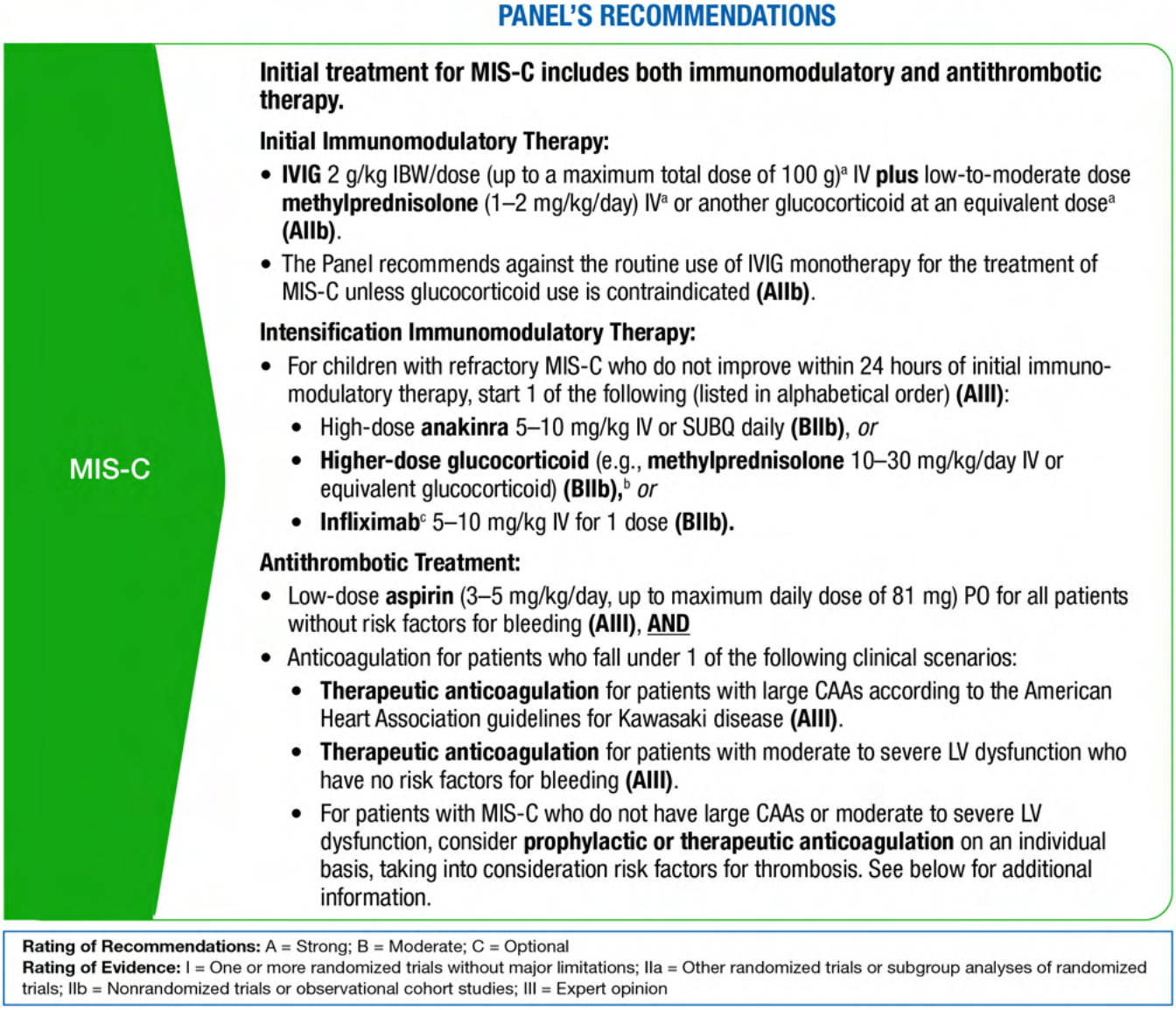
This section outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the therapeutic management of pediatric patients with multisystem inflammatory syndrome in children (MIS-C). The Centers for Disease Control and Prevention's (CDC) case definition for MIS-C includes "an individual aged <21 years."[1] The recommendations in this section encompass this age group. There are no randomized controlled trials that compare treatment approaches for MIS-C. However, data from descriptive and observational comparative effectiveness studies are available to guide treatment for MIS-C. For information on the clinical manifestations of MIS-C, see Special Considerations in Children.

Multisystem Inflammatory Syndrome in Adults

It should be noted that adults can present with a syndrome similar to MIS-C, termed multisystem inflammatory syndrome in adults (MIS-A).[2] The published literature on MIS-A is restricted to small case series that provide little data to guide treatment decisions for patients with MIS-A.[3] Although Panel members extrapolate from MIS-C data to aid in the management of individuals with MIS-A, it should be emphasized that this approach to managing MIS-A has not been studied.

Figure 3. Therapeutic Management of Hospitalized Pediatric Patients With MIS-C



[a] Duration of therapy may vary. See duration in table and text below.

[b] In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose glucocorticoids and infliximab or anakinra. Anakinra and infliximab **should not be given** in combination.

[c] Infliximab **should not be used** in patients with macrophage activation syndrome.

Key: CAA = coronary artery aneurysm; IBW = ideal body weight; IV = intravenous; IVIG = intravenous immunoglobulin; LV = left ventricular; MIS-C = multisystem inflammatory syndrome in children; PO = oral; SUBQ = subcutaneously

Table A. Dosing Regimens for the Drugs Recommended for the Treatment of MIS-C

Drug Name	Dosing Regimens *For infants, children, and adolescents unless otherwise specified. The doses listed are for FDA-approved indications for other diseases or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters
Intravenous Immunoglobulin	• IVIG 2 g/kg IBW/dose (up to a maximum total dose of 100 g) IV for 1 dose • In the event of cardiac dysfunction or fluid overload, consider administering IVIG in divided doses (1 g/kg IBW/dose IV every 24 hours for 2 doses).	• Hypersensitivity • Fever • Chills • Flushing • Hemolytic anemia	• Renal function • Urine output • CBC with differential • Infusion or injection-related AE • Anaphylaxis • Signs and symptoms of hemolysis
Methyl-prednisolone	• Methylprednisolone 1 to 2 mg/kg/dose IV every 12 hours • If the patient with MIS-C does not respond to 1–2 mg/kg/dose IV every 12 hours, increase the dose to 10–30 mg/kg/day (up to maximum of 1,000 mg/day) IV for 1 to 3 days.	• Adrenal suppression • Hyperglycemia • Sodium retention • Fluid retention • Leukocytosis • Immune suppression	• Blood pressure • CBC with differential • BMP
Anakinra	Anakinra 5–10 mg/kg/day IV (preferred) or SUBQ in 1 to 4 divided doses	• Headache • Fever • Hypersensitivity • Immune suppression • Transaminitis	• CBC with differential • LFTs • Scr
Infliximab	Infliximab 5–10 mg/kg/dose IV for 1 dose	• Infusion-related reaction • Headache • Immune suppression	• Monitor vital signs every 2–10 minutes during infusion • CBC with differential
Aspirin	Aspirin 3–5 mg/kg/dose (up to maximum of 81 mg/dose) PO once daily	• Gastrointestinal ulcers • Hypersensitivity • Renal dysfunction	• Signs or symptoms of bleeding • Renal function
Enoxaparin	**Enoxaparin Prophylaxis** *Aged >2 Months to <18 Years:* • 0.5 mg/kg/dose (up to maximum of 30 mg/dose) SUBQ every 12 hours **Enoxaparin Treatment** *Aged >2 Months to <18 Years:* • 1 mg/kg/dose SUBQ every 12 hours • Monitor antifactor Xa activity (treatment goal: 0.5 to 1).	• Increased risk of bleeding • Thrombocytopenia	• CBC with differential • Renal function

Key: AE = adverse effect; BMP = blood mineral panel; CBC = complete blood count; FDA = Food and Drug Administration; IBW = ideal body weight; IV = intravenous; IVIG = intravenous immunoglobulin; LFT = liver function test; MIS-C = multisystem inflammatory syndrome in children; PO = orally; Scr = serum creatinine; SUBQ = subcutaneously

Treatment Considerations for Children With MIS-C

Initial Immunomodulatory Therapy for MIS-C

The Panel recommends consultation with a multidisciplinary team when managing immunomodulating therapy for children with MIS-C **(AIII)**. The multidisciplinary team may include experts in cardiology, hematology, infectious disease, intensive care, and rheumatology. MIS-C is defined by multiorgan dysfunction, and input from other pediatric subspecialists may be needed depending on the presentation of the individual patient. Thus, children with MIS-C should be cared for at centers with access to these pediatric specialists.

Intravenous immunoglobulin (IVIG) and glucocorticoids are the most commonly used immunomodulatory medications in reported cohorts of children with MIS-C.[4-12] The American College of Rheumatology has outlined initial diagnostic and treatment considerations in MIS-C and recommends IVIG in combination with glucocorticoids as first-tier therapy for most hospitalized children with MIS-C.[13] Multiple nonrandomized studies suggest that front-line IVIG in combination with glucocorticoids is associated with less treatment failure, faster recovery of cardiac function, shorter intensive care unit (ICU) stay, and decreased requirement for treatment escalation compared to IVIG monotherapy.[5,14-17] Based on these data, the Panel recommends using **IVIG** in combination with low-to-moderate-dose **glucocorticoids** for children hospitalized with MIS-C **(AIIb)**. The Panel recommends against the routine use of IVIG monotherapy for the treatment of MIS-C unless glucocorticoid use is contraindicated **(AIIb)**.

IVIG should be given at a dose of 2 g/kg of ideal body weight up to a maximum dose of 100 grams. The patient's cardiac function and fluid status should be monitored carefully during the IVIG infusion. IVIG can be given in divided doses of 1 g/kg of ideal body weight over 2 days if there is a concern about the patient's fluid status. Methylprednisolone 1 to 2 mg/kg/day, or another glucocorticoid at an equivalent dose, is considered low-to-moderate glucocorticoid dosing. Once there is clinical improvement (i.e., the child is afebrile, end organ dysfunction resolves, and inflammatory markers are trending downward), a steroid taper should be initiated. Typically, the taper lasts for several weeks to avoid rebound inflammation and is guided by the clinical status of the patient.

There remains uncertainty regarding the use of glucocorticoid monotherapy versus IVIG plus glucocorticoids as initial therapy for MIS-C because comparative studies evaluating these 2 treatment approaches have not been conducted. There are limited published data on long-term outcomes in children with MIS-C who were treated with initial glucocorticoid monotherapy. Due to the risk of coronary artery aneurysms in patients with MIS-C, and the proven benefit of IVIG in reducing the frequency of coronary artery aneurysms in patients with Kawasaki disease, many clinicians continue to incorporate IVIG into the treatment regimen for MIS-C.[12,18] Currently, there is insufficient evidence for the Panel to recommend either for or against the use of glucocorticoid monotherapy for MIS-C.

Summary of Published Data on Initial Immunomodulatory Therapy for MIS-C

Intravenous Immunoglobulin in Combination With Glucocorticoids

No randomized clinical trials evaluating IVIG plus glucocorticoids for the treatment of MIS-C have been completed. The comparative benefit of adding steroids to IVIG for MIS-C treatment has been estimated in observational cohorts using statistical techniques to adjust for confounders. The first of these studies employed observation data from a national surveillance system cohort in France and used propensity matching to compare short-term outcomes in children with MIS-C who were treated initially with IVIG (2 gm/kg) alone or IVIG and methylprednisolone (most patients received 1.6–2 mg/kg/day for 5 days).[14] The study team observed a lower risk of treatment failure (defined as persistence of fever 2 days after

treatment or recurrent fever within 7 days), lesser requirement for hemodynamic support, less severe left ventricular dysfunction, and shorter ICU stays among the children initially treated with the combination therapy.[14] This was a small study, and only 32 patients treated with IVIG and methylprednisolone and 64 patients treated with IVIG alone could be matched based on propensity score.

A larger study in the United States analyzed data from the Overcoming COVID-19 surveillance registry to evaluate immunomodulatory therapy for MIS-C. Initial treatment with IVIG plus glucocorticoids (n = 103) was associated with a lower risk of cardiovascular dysfunction (measured using a composite outcome of left ventricular ejection fraction of <55% or vasopressor use) on or after Day 2 compared to treatment with IVIG alone in an equal number of propensity score-matched patients. The composite outcome occurred in 17% of the patients in the IVIG plus glucocorticoids group versus 31% of the patients in the IVIG alone group (risk ratio 0.56; 95% CI, 0.34–0.94).[15] In addition, patients treated with the combination of IVIG and glucocorticoids were less likely to require adjunctive immunomodulatory therapy than those treated with IVIG alone. Methylprednisolone, the most prescribed glucocorticoid, was administered to 353 patients (68% of the patients, including nonpropensity matched patients, in the entire cohort). Among these patients, the dosing of methylprednisolone ranged from 2 mg/kg/day in 284 patients (80%) to 10 to 30 mg/kg/day in 69 patients (20%).

A third study, the international and pragmatic BATS study, compared patients with MIS-C who received IVIG alone (n = 246) to those who received IVIG and glucocorticoids (n = 208). This study found similar rates for the composite outcome of inotropic support or mechanical ventilation by Day 2 or later or death in both treatment arms. The outcome occurred in 44 of 221 participants (21%) in the IVIG alone arm versus 56 of 180 participants (31%) in the IVIG plus glucocorticoids arm (OR 0.77; 95% CI, 0.33–1.82). However, escalation of immunomodulatory treatment was less common among the patients who received IVIG plus glucocorticoids than among those who received IVIG alone (OR 0.18; 95% CI; 0.10–0.33). This study was notable for including patients with suspected MIS-C (i.e., patients who did not meet CDC or World Health Organization [WHO] criteria for MIS-C) and voluntary reporting of included cases by pediatricians. This multicenter study included sites from 34 counties with potential for more variability in supportive care. In addition, the overall percentage of patients with abnormal cardiac findings (12% of the 538 patients) was lower than in other cohorts.[16]

Intravenous Immunoglobulin Monotherapy

The use of IVIG is long established for Kawasaki disease, a syndrome that has overlapping manifestations with MIS-C, and thus the product's safety profile is well understood. In Kawasaki disease, IVIG prevents the development of coronary artery aneurysms,[18,19] a complication also observed in some patients with MIS-C. IVIG is the most frequently used therapy for MIS-C. In a national survey of U.S. institutional protocols for managing MIS-C, IVIG was the first-line therapy in 98% of 40 participating centers.[20]

Data on the efficacy of IVIG in MIS-C is extrapolated from case series that show mostly favorable outcomes. In a series of 539 MIS-C cases, 77% of the children received IVIG. A sizeable proportion of these children had reduced left ventricular ejection fraction at admission (172 of 503 evaluable patients [34.2%]); the symptom resolved by Day 30 in 156 of the children (90.7%). Although these studies have not described the occurrence of specific adverse events related to IVIG use, the dosing used (IVIG 2 g/kg) has a well-established safety profile when used for Kawasaki disease.[12]

A limitation of all published studies on IVIG use for MIS-C is the frequent and often rapid sequential addition of other immunomodulatory therapies, such as corticosteroids. In addition, there is accumulating evidence that glucocorticoids given in combination with IVIG are more effective as treatment for MIS-C (see discussion above). However, IVIG monotherapy may be a reasonable

treatment option for a small subset of patients with MIS-C who are stable (i.e., not in shock or with organ-threatening disease) and have contraindications to glucocorticoid therapy. Such contraindications may include concern about the impact on diagnostic evaluation or on the underlying medical condition.

Glucocorticoid Monotherapy

The BATS study described above also evaluated initial treatment with IVIG (n = 246) compared to glucocorticoids (n = 99) and found no differences in primary or secondary outcomes between these 2 cohorts.[16] However, in a subgroup analysis of patients who met the WHO criteria for MIS-C, the glucocorticoid alone group (n = 78) had significantly fewer patients who required respiratory support by Day 2 or later or who died than the IVIG alone group (n = 192).

The BATS study has several limitations. The length of follow-up in this study was not clearly defined, and most outcome measures were evaluated around Day 2 of treatment. Rates of coronary artery aneurysms and myocardial dysfunction and scarring as long-term outcomes were not reported. Further, many patients received additional immunomodulatory agents after Day 1, including 47 patients in the initial glucocorticoids alone group who also received IVIG. This study did not compare initial therapy with glucocorticoids alone versus IVIG in combination with glucocorticoids. Further studies are needed to replicate these findings and to evaluate the long-term outcomes in patients with MIS-C treated with glucocorticoids alone.

Intensification Immunomodulatory Therapy for MIS-C

Children with MIS-C typically respond briskly to immunomodulatory therapy and show clinical improvements within the first 24 hours of treatment. Treatment response is characterized by resolution of fever, improvement of organ function, and reduced levels of inflammatory markers, particularly C-reactive protein. By contrast, refractory disease is often accompanied by persistent fever, worsening organ dysfunction, and increasing levels of inflammatory markers. **Intensification therapy** is recommended for children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy **(AIII)**. Children with uncontrolled MIS-C despite treatment with IVIG and low-to-moderate-dose glucocorticoids will often continue to deteriorate without further intervention, and this decline in clinical status can be quite rapid.

There are no comparative studies evaluating intensification therapies for MIS-C. Available data on this topic are limited to results from cohort studies in patients with MIS-C, expert opinion, and experience in treating other hyperinflammatory syndromes in children, such as Kawasaki disease and macrophage activation syndrome. For children with refractory MIS-C, the Panel recommends additional immunomodulatory therapy (in alphabetical order) with **anakinra (BIIb)**, higher-dose **glucocorticoids (BIIb)**, or **infliximab (BIIb)**. Currently, there is insufficient evidence to determine which of these agents is most effective for intensification therapy in patients with refractory MIS-C. In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose **glucocorticoids** and **anakinra (BIII)** or higher-dose **glucocorticoids** and **infliximab (BIII)**. Anakinra and infliximab **should not be used** in combination. A second dose of IVIG is not commonly reported in the literature as a strategy for intensification therapy in MIS-C. This may be due to the high rates of IVIG resistance, the rapid pace of disease escalation, and the risk for fluid overload in MIS-C patients.[8] Therefore, the Panel **recommends against** a second dose of **IVIG** for intensification therapy in patients with refractory MIS-C **(BIII)**.

Patients with MIS-C who receive multiple immunomodulatory agents are at risk for infection and need to be monitored carefully. Most children with MIS-C were previously healthy. In patients who have an immune disorder or are taking immunosuppression therapy, the risk of infection is greater. The risks and benefits of treating immunocompromised MIS-C patients with immunomodulatory agents need to be evaluated on a case-by-case basis.

Summary of Published Data for Intensification Immunomodulatory Therapy for MIS-C

High-Dose Glucocorticoids

High-dose glucocorticoid therapy is defined as methylprednisolone (or an equivalent corticosteroid) dosed at 10 to 30 mg/kg/day given intravenously (IV). Often, this higher dose of glucocorticoids is given for 1 to 3 days with a subsequent return to low-to-moderate dosing (1–2 mg/kg/day). Multiple observational studies have reported the use of high-dose glucocorticoids (methylprednisolone 10–30 mg/kg/day) in children with MIS-C.[15,21-23] In addition, single-center treatment protocols for MIS-C that incorporate high-dose glucocorticoids into the treatment algorithm have been published. Implementation of the protocols has resulted in positive clinical outcomes in patients with MIS-C.[17] There is substantial experience using high-dose glucocorticoids in pediatric patients with other inflammatory conditions, such as Kawasaki disease and macrophage activation syndrome.

Anakinra

Anakinra is the most commonly used biologic medication for the treatment of MIS-C in the United States.[20] Multiple, noncomparative, observational cohorts have reported on the use of anakinra in patients with MIS-C.[8,9,11] This medication has been used extensively with a good safety record in pediatric patients with other hyperinflammatory syndromes (e.g., systemic juvenile idiopathic arthritis, macrophage activation syndrome).[24-26] Anakinra has also been used successfully to treat IVIG-resistant Kawasaki disease. Anakinra has a short half-life (4–6 hours), and the medication can be stopped quickly, which many providers regard as a benefit relative to longer-acting immunomodulators. High-dose anakinra (5–10 mg/kg/day) is recommended for MIS-C based on the improved efficacy of anakinra used at higher doses for macrophage activation syndrome. The duration of anakinra therapy varies in the literature and is used by some patients for long periods (e.g., up to 2 weeks) as a steroid sparing agent.

Infliximab

The Panel recommends a single dose of infliximab 5 to 10 mg/kg IV as an option for intensification therapy. Infliximab has been studied for the treatment of MIS-C in a single-center retrospective study that compared patients treated with IVIG alone (n = 20) to those treated with IVIG and a single dose of infliximab 10 mg/kg IV (n = 52).[27] Of note, infliximab was used as first-line therapy in this study, and the patients were not treated with glucocorticoids. The patients who received IVIG and infliximab were more likely to be admitted to the ICU and had more severe illness than those who received IVIG alone. Yet, the patients who received the combination therapy were less likely to require additional therapy after 24 hours (the primary outcome). In addition, patients who received IVIG and infliximab had shorter admissions to the ICU and less cardiac dysfunction. These results show that infliximab has a therapeutic effect in MIS-C. Infliximab is approved by the Food and Drug Administration for use in children with inflammatory bowel disease and is used widely to treat juvenile idiopathic arthritis. Infliximab has been employed in IVIG-resistant Kawasaki disease.[28,29] Although the half-life of infliximab in MIS-C is unknown, it likely has effects that persist for several weeks. This extended period of drug activity can allow for a steroid-sparing effect in MIS-C.

Antithrombotic Treatment for MIS-C

There is general agreement that patients with MIS-C who do not have risk factors for bleeding should receive low-dose aspirin **(AIII)**. This recommendation is largely due to experience in children with Kawasaki disease and the likelihood of analogous platelet activation and endothelial dysfunction in children with MIS-C.[30] Children treated with aspirin and steroids should also receive gut protection. Patients with MIS-C who have large coronary artery aneurysms (Z-score ≥10) should receive therapeutic anticoagulation according to the American Heart Association guidelines for Kawasaki disease **(AIII)**. Children with left ventricular dysfunction are at risk for intracardiac thrombosis. Patients with MIS-C

and moderate-to-severe left ventricular dysfunction should receive therapeutic anticoagulation, unless contraindicated due to bleeding risk factors **(AIII)**.

There is less consensus on the use of either prophylactic or therapeutic anticoagulation in patients with MIS-C who do not have large coronary artery aneurysms and/or moderate-to-severe left ventricular dysfunction. Children with MIS-C have marked elevations in D-dimer levels and other abnormalities of coagulation, which suggests that they may be at increased risk for thrombosis.[31] In 1 study of children with acute COVID-19 and MIS-C, indwelling catheters, older age (>12 years), malignancy, admission to the ICU, and elevated D-dimer levels were all independent risk factors for thrombosis.[32] There is less known about the risk of bleeding in children with MIS-C who are treated with anticoagulation. Major bleeding events have been reported in MIS-C patients treated with anticoagulation.[32] Given the uncertainty regarding the benefit of anticoagulation for MIS-C, prophylactic or therapeutic anticoagulation for children with MIS-C who do not have large coronary artery aneurysms or moderate-to-severe left ventricular dysfunction should be considered on a case-by-case basis, taking into account the risk factors for thrombosis.

Antiviral Therapy in MIS-C

The role of antiviral therapy in treating MIS-C has not been systematically studied; however, it is not expected to be beneficial because MIS-C is considered an immune-mediated phenomenon that occurs weeks after a primary SARS-CoV-2 infection. Therefore, the Panel **recommends against** the use of **remdesivir** for patients with MIS-C **(AIII)**.

Critical Care Management

Shock occurs in approximately 50% of patients with MIS-C, and may include elements of distributive, cardiogenic, or hypovolemic shock.[12,33,34] In general, clinicians should manage shock in patients with MIS-C per the usual critical care standards as outlined in the Pediatric Surviving Sepsis Campaign Guidelines.[35]

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